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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/788,731	02/27/2004	Jason R. Fink	58210US004	6098

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EXAMINER	
HAMUD, FOZIA M	

ART UNIT	PAPER NUMBER
1647	

NOTIFICATION DATE	DELIVERY MODE
11/29/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/788,731	FINK ET AL.	
	Examiner	Art Unit	
	Fozia M. Hamud	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,9-22,25-34 and 56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 9-22, 25-34, 56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Continued Examination:

1a. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 04 September 2007 has been entered.

Status of Claims:

1b. Claims 4-8, 23-24 and 35-55 have been cancelled. Claims 1-3, 9-22, 25-34 and 56 are pending and under consideration.

Response to Applicant's Argument:

2. The following rejections are withdrawn in light of Applicant's arguments:

2a. The rejection of claims 1 and 25 made under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, by introducing new matter into the claims is withdrawn, because Applicants' argument that the cells used in examples 3 and 4 were peripheral blood mononuclear cells (PBMCs), obtained from human whole blood is found persuasive. Furthermore, U.S. Patent 6,667,312, which was incorporated by reference in the instant speciation, describes PBMCs as being drawn from human subjects, (see column 90, lines 53-65).

Maintenance of rejections:

Claim Rejections - 35 U.S.C. § 112:

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3a. The rejection of claims 1-3, 9-22, 25-34 and 56 made under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is maintained for reasons of record, set forth in the office actions.

Applicants submit that claim 1 and claims that depend from it meet the requirements of 35 U.S.C. § 112, second paragraph, because one skilled in the art is aware of a multitude of different assays (e.g., cytokine secretion, co-stimulatory marker production, functional assays, etc.) that can be employed to detect whether and to what extent a compound modulates TLR7 or TLR.8 mediated cellular activity. The assays, how to perform the assays, and the endpoint (that which is being measured) for each assay are well known to those skilled in the art.

Applicants argue that claim 9 has been amended to recite steps that include providing an assay to detect modulation of a first TLR-mediated cellular activity and an assay to detect modulation of a second TLR.-mediated cellular activity, performing the assay to detect modulation of the first TLR. mediated cellular activity using the test compound, performing the assay to detect modulation of the second TLR mediated cellular activity using the test compound, and determining the extent to which the test compound modulates each TLR- mediated cellular activity. Applicants submit that as noted with regard to claim 1, the assays, how to perform the assays, and the endpoint (that which is being measured) for each assay are well known to those skilled in the art.

With regard to claim 25, Applicants contend that one skilled in the art would, indeed, know which cell populations naturally express TLR7 and/or TLR8. Claim 25 does not recite testing the activity of the compound, rather, claim 25 recites a method that makes practical use of the observation that certain TLR agonists modulate TLR-mediated cellular activity to varying degrees. Thus, claim 25 contemplates having knowledge of a plurality of TLR agonist compounds, knowing the TLR modulation profile of each compound, and knowing the desired TLR-mediated cellular activities one wishes to modulate. One skilled in the art can then select the compound that modulates TLR7-mediated cellular activity and TLR8-mediated cellular activity in the desired fashion to achieve the desired mix of TLR- mediated cellualr activities from a human immune cell population, and then obtain that desired mix of TLR-mediated cellular activities by contacting the selected compound with the immune cell population.

These arguments have been considered, but are not deemed persuasive. The premise of the instant invention is that Applicants discovered that TLR7 and TLR8 regulate different innate human cells. Applicants showed that human Myeloid dendritic cells (mDCs) are activated by a TLR7/8 agonist and a TLR8-selective agonist, but are not activated by a TLR7-selective agonist, while human Plasmaeytoid dendritic cells (pDCs), on the other hand, are activated by a TLRT7/8 agonist and a TLR7 selective agonist, but not a TLR8-selective agonist. It is correct that the skilled artisan might be able to recognize assays to detect whether a specific compound stimulates or inhibits certain cellular activities that is mediated by either TLR7 or TLR8. The phrase "TLR mediated cellular activity" recited in claim 1 is indefinite, because, not all the cellular

activities that are mediated by TLR7 or TLR8 are disclosed by the instant specification and they are all not known in the art. Claim 1, is also vague and indefinite, because it lacks positive steps and it also lacks proper controls. It is unclear, how would the skilled artisan know whether the changes that the test compound causes is through TLR7 or TLR8 or through some other receptor.

Regarding claim 9, It is acknowledged that the skilled artisan can identify whether a compound is an agonist or an antagonist of a particular toll like receptor, (TLR), and whether said compound modulates, i.e, stimulates or inhibits a cellular activity mediated by said TLR, from the known properties of the compound. However, the claim is indefinite, because which TLR mediated cellular activities to assay for is unclear. Claim 9 is also rendered vague because of the recitation of "TLR modulation profile", because the metes and bounds of this phrase cannot be ascertained. Furthermore, Applicants have not described to what "extent" is "cellular activity" be modulated. There is no upper limit as to the extent of said modulation. This claim also lacks proper controls. Furthermore, if the TLR modulation profile" of the test compound is already known, what is the point of testing it? It is, therefore, unclear what claims 9-24 add to the already known information about said compound. Claim 9 is ambiguous, because the objective of this claim cannot be ascertained.

With respect to claims 25-33 and 56, Claim 25 does not recite testing the activity of the compound, rather, claim 25 recites a method that makes practical use of the observation that certain TLR agonists modulate TLR- mediated cellular activity to varying degrees. Thus, claim 25 contemplates having knowledge of a plurality of TLR

agonist compounds, knowing the TLR modulation profile of each compound, and knowing the desired TLR-mediated cellular activities one wishes to modulate. One skilled in the art can then select the compound that modulates TLR7-mediated cellular activity and TLR8-mediated cellular activity in the desired fashion to achieve the desired mix of TLR- mediated cellular activities from a human immune cell population, and then obtain that desired mix of TLR-mediated cellular activities by contacting the selected compound with the immune cell population.

With respect to claims 25-33 and 56, again "TLR-mediated cellular activity" is vague, no recitation of which cellular activity, how to test said activity and what is the expected result. The claim does not specify which cell populations to be used and what are the differences of these populations. Applicants must identify which cells to use, what the assay for.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4a. Claims 1-3, 25-34 and 56 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, for reasons of record. Claims 9-22 are not included in this rejection, because no meaningful interpretation can be attributed for these claims 9-24.

Applicants ague that one skilled in the art recognizes that a multitude of routine, well known assays can be employed to determine whether and to what extent a compound modulates TLR-mediated cellular activity. The assays, how to perform the

assays, and the endpoint (that which is being measured) for each assay are well known to those skilled in the art.

This argument has been considered, but is not found persuasive. Applicants identified that TLR7 and TLR8 regualte different human immune cells, namely, that human Myeloid dendritic cells (mDCs) are activated by a TLR7/8 agonist and a TLR8-selective agonist, but are not activated by a TLR7-selective agonist, while human Plasmaeytoid dendritic cells (pDCs), on the other hand, are activated by a TLRT7/8 agonist and a TLR7 selective agonist, but not a TLR8-selective agonist. Applicants measured the expression of specific cytokines or costimulatory proteins.

The claims are broad because of the recitation "TLR-mediated cellular activity", this encompasses known and yet to be discovered activities, and the instant specification. The instant specification also does not enable 'all possible' human cells that naturally express TLR7 or TLR8. The specification discloses two specific human cells, Plasmaeytoid dendritic cells (pDCs) and Myeloid dendritic cells (mDCs) ,that naturally express either TLR7 or TLR8, respectively, and this does not enable the genius of all possible human cells that express said receptors. Finally it is the specification, not the knowledge of the skilled artisan that must supply the novel aspects of the invention.

Genentech Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1366, 42 USPQ2d 1001, 1005 (Fed. Cir. 1997): " It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement". The Genentech court also held that ["(P)atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention". Id. In this case, Applicant is expecting others to identify

regions other than those disclosed in Figure 3 that are critical for pathogen resistance, and determine which among infinite possible modifications would retain the desired activity, and then test those modified variants through the myriad of transgenic plants transformed with each of the modified variants to identify which would induce enhanced disease resistance.

Accordingly, the disclosure does not enable the methods claimed in claims 1-3, 25-33 and 56.

Claim rejections-35 USC § 103:

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1-3, 25-33 and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hornung et (The journal of Immunology, October 2002, Vol. 168, pages 4531-4537, cited in the IDS od 13 August 2004) in view Gibson et al, (cellular Immunology, August 2002, Vol. 218, pages 74-86).

It is understood that instant claims 1-3 are drawn to a method of identifying a compound that selectively modulates at least one TLR-mediated activity, by using

human cells that express TLR7 or TLR8, while claims 25-33, and 56 are directed to a method of modulating human immune cells that express TLT7 or TLR8. No meaningful interpretation can be obtained for claims 9-24, because the disclosure does not describe or teach how to identify a "TLR modulation profile".

Hornung et al teach that human Plasmaeytoid dendritic cells (pDCs) express TLR7 while human moncoytes express TLR8, (see page 4533, bottom of column 2).

However, Hornung et al do not teach a method of identifying compounds that modulate TLR7 or TLR8 by using said cells.

Gibson al teach that TLR7 agonists stimulate human plasmacytoid dendritic cells (pDC) to produce a number of cytokines including TNF-α, IP-10, interferon-α and interferon-ω, (see page 78, figure 4). The authors show that certain compounds activate NF-kB through TLR7, (see table 2). Gibson et al teach a method of screening for compounds that modulate a TLR-mediated cellular activity (e.g TNF-α, IP-10,) and provide a means of testing this effect.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the instant invention was made to combine the teachings of Hornung et al and Gibson et al and develop a method for screening compounds that modulate TLR7 or TLR8, because Hornung et al teach human cells that express these receptors and Gibson et al teach a method for screening. It would also be obvious to use compounds identified in the screening method to modulate the human cells that express TLR7 or TLR8. One would have expected success because references teach human cells that express TLR7 or TLR8 and methods of testing for activity.

One of ordinary skill in the art would have been motivated to combine the teachings of the Hornung et al and Gibson et al, because toll like receptors play an important role in infection and induction of pro-inflammatory cytokines, and studying these receptors is of utmost importance in understanding infection and how to treat it. .

Conclusion:

6. No claim is allowed.

Advisory Information:

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fozia M. Hamud whose telephone number is (571) 272-0884. The examiner can normally be reached on Monday-Friday: 8:00 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Fozia M Hamud/
Examiner, Art Unit 1647
25 November 2007